

ASH meeting features St. Jude research on gene therapy, cancer genetics and blood diseases

Preview St. Jude reports on gene therapy for 'bubble boy' disease, cancer genetics, cognitive function and sickle cell disease, beta thalassemia and more, including honors and updates on leading-edge topics

(MEMPHIS, Tenn. – Dec. 9, 2017) St. Jude Children's Research Hospital researchers will report on advances in gene therapy, sickle cell disease, cancer genetics and more at the 59th Annual Meeting of the American Society of Hematology (ASH). The four-day meeting begins Saturday, Dec. 9, in Atlanta.

James R. Downing, M.D., St. Jude president and chief executive officer, will receive the 2017 E. Donnall Thomas Prize for his pioneering research to advance understanding of the molecular genetics that underlie pediatric acute leukemia. The work has laid the foundation for individualized treatments that give children the best chance for cures.

As part of the honor, Downing will present a lecture titled "The Molecular Pathology of Pediatric Acute Leukemia." The lecture is set for Monday, Dec. 11, at 9 a.m. ET in the Georgia World Congress Center, Building C, Hall C2-3.

Promising preliminary results of a St. Jude—led study of gene therapy for infants with X-linked severe combined immunodeficiency will be featured in the meeting's press program. The press conference is set for Saturday, Dec. 9, at 9 a.m. ET. Ewelina Mamcarz, M.D., an assistant member of the St. Jude Department of Bone Marrow Transplantation and Cellular Therapy, will report on the first six infants to receive gene therapy with a safety-modified lentiviral vector developed at St. Jude combined with low-dose chemotherapy.

The work of St. Jude postdoctoral and clinical fellows plus a medical student is also being recognized. Zhaohui Gu, Ph.D., a St. Jude postdoctoral fellow, will be recognized with the ASH Fellow Scholar Award in basic/translational research. Harry Lesmana, M.D., a St. Jude clinical hematology/oncology fellow, will be recognized with an ASH Abstract Achievement Award. Anjelica Saulsberry was selected for the Minority Medical Student Award Program. Saulsberry is a University of Tennessee Health Sciences Center medical student who works with Jane Hankins, M.D., an associate member of the St. Jude Department of Hematology.

St. Jude researchers will also give talks, participate in panels and moderate sessions on a range of topics throughout the meeting and in the Friday, Dec. 8, satellite session. The subjects include emerging tools for genomic data analysis, cancer survivorship, pediatric cancer predisposition and genome editing for treatment of sickle cell disease and beta thalassemia.

St. Jude research will also be featured in oral presentations and at poster sessions.

A summary of the oral presentations:

**Saturday, Dec. 9,
7:45 a.m. ET**

Building B, B405-407

Abstract 31

***TP53* variation is common in high-risk pediatric leukemia subtype**

Maoxiang Qian, Ph.D., a St. Jude postdoctoral fellow, will report evidence Saturday, Dec. 9, from the laboratory of Jun J. Yang, Ph.D., suggesting that about 1 percent of childhood acute lymphoblastic leukemia cases are related to germline genetic variations in the *TP53* tumor suppressor gene. The variations are also associated with a greater risk for poor patient outcomes, including as much as a 1-in-4 chance of developing second cancers.

“These *TP53* variants are a real double whammy,” said Yang, an associate member of the St. Jude Department of Pharmaceutical Sciences. “Not only are the children who carry them more likely to develop leukemia, they are also more likely to die of their disease or treatment-related complications.”

Targeted sequencing of *TP53* in 3,858 children with ALL led to identification of 22 high-risk *TP53* variants along with additional variants that merit further study. Children with the variants were more likely to be older when their cancer was diagnosed and far more likely to have the high-risk subtype hypodiploid ALL. The patients were enrolled in clinical trials organized by the Children’s Oncology Group, a clinical research cooperative.

These are germline variations carried in the DNA of every cell and are usually inherited. The findings add to evidence that some ALL is linked to Li-Fraumeni syndrome, a rare familial cancer predisposition syndrome caused by inherited mutations in *TP53*.

In this study, patients with the high-risk *TP53* variants were about three times less likely to survive their disease and had as much as a 25 percent chance of developing a second cancer.

“These findings have clinical significance for survivors and physicians in terms of both treatment and after-therapy surveillance,” Yang said.

Sunday, Dec. 10

8 a.m. ET

Building B, B213-214

Abstract 285

Research reveals possible new approach to beta thalassemia treatment

Sunday, Dec. 10, a St. Jude scientist will outline a possible new approach to beta thalassemia treatment that uses drugs to rescue red blood cells by reducing the toxic buildup of hemoglobin components.

Hemoglobin is the protein red blood cells use to carry oxygen in the body. Normal hemoglobin includes four protein chains—two alpha globin and two beta globin. Patients with beta thalassemia inherit mutations that reduce beta globin synthesis, causing alpha globin to accumulate. Without its normal beta globin partner, excessive alpha globin is toxic to red blood

cells. Ultimately, excessive alpha globin kills red blood cells, resulting in anemia and other sometimes life-threatening symptoms associated with beta thalassemia.

Researchers have identified an enzyme, Ulk1, that works in red blood cells to eliminate excess alpha globin through autophagy, a process that cells use to degrade unwanted proteins. When Ulk1 was knocked out in mice with beta thalassemia, there was a two-fold increase in damaging alpha globin, with decreased red blood cell survival. Treatment of beta thalassemic mice with a drug predicted to enhance Ulk1 activity accelerated alpha globin degradation, and red blood cell lifespan improved.

Investigators showed that currently available drugs, including the immune suppressive agent rapamycin (Pfizer's RAPAMUNE®), work indirectly to bolster Ulk1 activity. That reduces accumulated alpha globin in mice with beta thalassemia.

“This study provides a fresh take on beta thalassemia and its treatment by approaching it as a disorder of protein aggregation, which we usually think of in the context of Alzheimer’s disease or other neurodegenerative disorders,” said the study’s senior author Mitchell Weiss, M.D., Ph.D., chair of the St. Jude Department of Hematology. The research will be presented by Christophe Lechauve, Ph.D., a staff scientist in Weiss’ laboratory.

Sunday, Dec. 10

4:30 p.m. ET

Building B, B213-214

Abstract 475

Mechanism identified that is at work in high-risk germline gene variation

Research from the St. Jude laboratory of Jun J. Yang, Ph.D., detailing how a germline variation in *GATA3* fuels development of a high-risk leukemia subtype will be presented Sunday, Dec. 10. The subtype is Philadelphia chromosome-like ALL (Ph-like ALL). The findings raise hopes for exploring novel strategies to improve survival of patients with the high-risk *GATA3* variants. The variants are more common in Hispanic Americans and other people with Native American ancestry.

Ph-like ALL accounts for as much as 15 percent of pediatric ALL and is associated with an elevated risk of relapse and death. The research included targeted sequencing of *GATA3* in 5,008 pediatric ALL patients. The patients were enrolled in the clinical trials of St. Jude and the Children’s Oncology group.

Researchers showed the *GATA3* variants serve as a switch to turn on *GATA3* gene expression. Overexpression of *GATA3* results in increased expression of a leukemia oncogene, *CRLF2*. The findings suggest that overexpression of *GATA3* sets the stage for rearrangement of *CRLF2*, which is the defining molecular feature in up to half of Ph-like ALL cases. “This is one piece of the larger Ph-like ALL puzzle, but it raises the possibility of developing novel therapies that

target the variants,” Yang said. Hui Zhang, M.D., Ph.D., formerly of St. Jude, will present the research.

Monday, Dec. 11

7:15 a.m. ET

Building C, C202-204

Abstract 560

A mutation yields clues for reversing drug resistance in relapsed ALL

Glucocorticoids are a cornerstone of leukemia treatment. Resistance to steroids such as dexamethasone is a common problem for treatment of pediatric acute lymphoblastic leukemia patients who relapse. Monday, Dec. 11, a postdoctoral fellow in the St. Jude lab of Charles Mullighan, M.D., MBBS, will outline a novel strategy for restoring glucocorticoid sensitivity in such patients.

The work builds on previous research from Mullighan’s laboratory and reports that *CREBBP* is the most commonly mutated gene identified to date in relapsed pediatric ALL. In this study, the gene was mutated in 21.2 percent of 174 relapsed B- and T-ALL patients. The patients were enrolled in the clinical trials of St. Jude and the Children Oncology Group.

CREBBP is an epigenetic regulator of gene expression. Mutated, the protein has been tied to glucocorticoid resistance. The enzyme works by attaching a chemical compound to DNA as well as to other proteins involved in gene regulation. Working in mice and human cells growing in the lab, researchers detailed how *CREBBP* mutations disrupt normal CREBBP activity and also cripple steroid functioning.

Investigators screened about 11,300 drugs and other compounds and showed how one (GNE-049) restored steroid sensitivity in human cells with the mutation. “This offers a possible model for developing precision medicines to target the mutations driving relapsed leukemia,” said Mullighan, a member of the St. Jude Department of Pathology. Yunchao Chang, Ph.D., will present the research.

Monday, Dec. 11

5:15 p.m. ET

Building B, B308-309

Abstract 760

Evidence suggests cognitive benefit from hydroxyurea

A St. Jude researcher will report Monday, Dec. 11, on evidence that the drug hydroxyurea may protect and possibly improve the cognitive functioning of school-aged children with sickle cell anemia. The study is among the first to demonstrate cognitive benefit from hydroxyurea, which is proven to reduce pain crises and other symptoms of the inherited blood disorder.

Researchers compared how 21 children and adolescents with sickle cell anemia scored on IQ and related tests before and one year after starting treatment with hydroxyurea. Investigators also tracked the performance on the same tests of 11 similar patients whose parents opted against hydroxyurea therapy. The patients were 7 to 18 years old.

The average IQ score increased almost 3 points in the treatment group, but declined slightly in patients who did not receive the drug. The hydroxyurea group tended to score higher on other cognitive measures, including working memory and processing speed. Reading comprehension and other skills also improved.

“This study provides another reason hydroxyurea should be offered to and taken by all sickle cell anemia patients,” said Winfred Wang, M.D., a member of the St. Jude Department of Hematology, who will present the research.

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St. Jude Children’s Research Hospital

St. Jude Children’s Research Hospital is leading the way the world understands, treats and cures childhood cancer, sickle cell disease and other life-threatening diseases. It is the only National Cancer Institute-designated Comprehensive Cancer Center devoted solely to children. St. Jude is ranked the No. 1 pediatric cancer hospital by U.S. News & World Report. Treatments developed at St. Jude have helped push the overall childhood cancer survival rate from 20 percent to 80 percent since the hospital opened more than 50 years ago. St. Jude freely shares the breakthroughs it makes, and every child saved at St. Jude means doctors and scientists worldwide can use that knowledge to save thousands more children. Families never receive a bill from St. Jude for treatment, travel, housing and food — because all a family should worry about is helping their child live. To learn more, visit stjude.org or follow St. Jude on social media at [@stjuderesearch](https://twitter.com/stjuderesearch).